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LEGAL AFFAIRS DEPARTMENT
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DATE MAILED:
09/21/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-19 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

**EXAMINER'S ACTION**

The Abstract is objected to. It gives no information on the compounds or what they used for.

The specification is objected to. Pages 203 have Journal citations without page numbers. There must be corrected or, if not deemed essential, deleted.

Figures 2-6 are objected to as not credible, absent some sort of explanation. These all show significant actions occurring at t=0 hour. How can anything have happened at no elapsed time? For example, Figure 6 shows for 1501R, that at t= 0, 94% of hydrolysis has already occurred!! As time goes on, the amount of hydrolysis actually goes down. How can that be taken credibly? Figure 5 shows hydrolysis of 105%. Likewise in Figure 2 for 4546R. Data to 1570R in Figure 4 is absurd-30% at 0.25 hour, but none at 0.5 hour.

Claims 1-19 are rejected, 35 USC 112, para. 1 and 35 USC 101 for lack of enabling utility. Several problems arise.

1. These compounds are allegedly useful as prodrugs of lisofylline. However, that compound fixes n at 4 and requires methyl groups at the other positions, and requires the hydroxyhexyl at the three position. These claims are not so limited (this does not apply to claim 14, which is so limited).

2. Applicants have presented no evidence that lisofylline actually is useful for anything.

3. The specification contains no useful daily dosage information. Two ranges are set forth on page 9, lines 3-5. The first is 0.1 to 1000. The second is .001 to 40 all in mg/kg. These are no explanations as to why two are given and hence which is right. One is not a preferred version of the other, because the second range is set 100 fold (using lower limit) or 25 fold (using upper figure) lower than the other. Further, both ranges are impossibly broad. The first is a 10,000 fold range; the second is 40,000 fold. These are so broad as to be of no practical value; Cf. In re Gardner 166 USPQ 138.

4. The notion that these compounds are all prodrugs is simply not credible. Ordinary ethers (eg. $XR_5$=alkyl) cannot be significantly hydrolyzed by the body, as the body does not have the enzymes or acidity to cleave them to any significant degree (this point does not apply to claim 14).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 10, 11, 15-17, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 93/17684.

Ex. 1 corresponds to n=4, $X(R_5)n$-CO-cyclic group, using the broadest definition of cyclic group (see point 22 below).

Claims 1-4, 6-8, and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by EP 286041.

Ex. 5 corresponds to $X(R_5)n=CH_3$, n=4.

Reference copies were provided in the parent.

Claims 1-4, 6-8, 10, 15, and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 20 of U.S. Patent No. 306,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the above claims are embracive of the ethers which are a major part of the claims of the parent.

Claims 1-8 and 10-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 26, and 27 of U.S. Patent No. 199368. Although the conflicting claims are not identical, they are not patentably distinct from each other because 199368 has the esters. For example, its page 51, species 3 corresponds to $R_4$=acetyl in this case.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term "carbohydrate" (for $R_4$) is indefinite. $R_4$ is monovalent. A carbohydrate has no valences. Thus, its meaning is unknown.

2. The term "amino acid" is indefinite. There is no single generally accepted definition of amino acid. Is $NH_2CH_2CH_2CH_2CO_2H$ included? Is paraminobenzoic acid? Is carbamic acid? Is N,N diphenyl glycine? Is aminomethanesulfonic acid? Is piperidineacetic acid? Is diaminoacetic acid?

3. "About 4" is indefinite. Does this include 3? 2? 1? Zero? Likewise, "about 8".

4. "Substituted" (e.g. at page 26, line 18) with what?

5. "Selectively stable" at the start of claim 1 is an unclear requirement. Selective to what? What kind of stability is involved? What level of selectivity is required and how is it to be measured?

6. The definition of Formula II is confused. It is called "aliphatic hydrocarbon". Yet:

a. It is not a hydrocarbon, since $R_4$ must contain oxygen.

b. It is not necessarily aliphatic, since claim 2 lists amino acids with rings (e.g. phenylalanine).

7. The purpose of "independently" on page 26, line 4 is most unclear. Since only one of $R_1$ or $R_2$ can be formula II, and the other cannot be, how can it be other than independently?

8. What is "the ester linkage" of page 26, lines 11-12. This presumably includes C(O)O-C*, but does it also include O-C(O)-C*? Does it include other types of ester acids e.g. carbothioic acids, e.g. C(S)O-C*? Phosphonic acid? Carboimidic acids?

9. The "heterocyclic group" of page 27, line 1 is vague and cannot possibly be enabled for such scope. It is unclear what the nature and number of the heteroatoms can be, nor what substituents are permitted, whether unsaturation can be present, etc.

10. "$C_{1-10}$ acetoxyl" (page 26, line 19) is unclear. Does applicant mean acetoxy or acetyl? Whichever choice is selected must be supported in the specification. Moreover, the "$C_{1-10}$" doesn't make sense, as there is no variable present.

11. "$C_{1-10}$" alkenyl and alkynyl is mistaken; $C_2$ is required. Likewise, $C_{1-6}$ alkenyl, etc.

12. "Amido" (page 27, line 15) is unclear. Is this $-C(O)NH_2$ or $-NHC(O)R$? Is it limited to amides of carboxylic acid? (e.g. is $-SO_2NH_2$ included)? Likewise "thioamido" etc.

13. The "primary, secondary, or tertiary $C_{1-6}$ hydroxy alkyl" is unclear. Do the adjectives refer to the carbon of attachment or the carbon bearing the OH?

14. "Carbonyl" as a substituent cannot be enabled. When attached to a carbon it forms a ketone (e.g. $R_5$=$-CH_3$ substituted becomes $R_5$=$-HC=C=O$) and ketenes are too toxic to use as pharmaceuticals. Likewise thiocarbonyl.

15. "Carboxylic acid" (page 27, line 17) is a molecule, not a moiety.

16. "Thio groups" (line 19, page 27) is of unknown meaning. Any group containing SH a thioether linkage, etc. could be a thio group.

17. "A single atom" is insupportable. Does this include Na? Tritium? Te?

18. What is "thioloxoalkyl"?

19. Sulfonyl and sulfoxyl would give e.g. $-HC=SO_2$ and $-C=S=O$, groups which are highly reactive and would be impossible for pharmaceuticals.

20. At page 27, line 18, what are the 3rd, 4th, and 5th terms?

21. Claim 9 is improperly dependent. The other-than formula II choice is limited in claim 1 to $C_{1-12}$ alkyl, which does not permit any oxygen atoms.

22. What does the "cyclic group" of page 27, line 1 require? Does the $R_5$ have to provide a cycle directly attached to X, or does this just mean a cycle anywhere? E.g. would $(CH_2)_4-P(O)(OPh)_2$ be a cyclic group? If the answer is yes, then the term is in this regard indefinite, and unsupported since nothing is said about what the rest of the moiety (the part which has no cycle) is. Thus, it is unclear whether this means, in effect "a group with a cycle" or "an (optionally substituted?) Group which is (other than substituent?) entirely cyclic "or what"?

23. The last 2 terms in claim 12 are of unknown meaning. Whatever meaning is selected must be supported by specification. Likewise, wherever else they may appear.

24. Page 27, line 29 says "cyclopropyl" but line 2 requires 4-7 atoms; hence claim 10 is improperly dependent and not enabled.

25. Page 27, line 32, next to last term is of unknown meaning.

26. Page 27, line 33, first 3 terms are unclear. Where is the alkyl? For example, is the methyl in second term on the benzene ring or the N of the amide?

27. Terms with "...benzenyl..." are indefinite. Presumably, either "...benzyl" or "...phenyl" is intended, but it is impossible to tell which (e.g. page 27, line 35).

28. $R_5$ should be defined as being independently selected, as clearly diverse $R_5$ groups are intended.

29. "Compound comprising" (line 1 of claim 1) is open ended; replacing "comprising" with "of" is suggested.

A facsimile center has been established in Group 1200, room 3C10. The hours of operation are monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine is (703) 308-4556 or 305-3592.

Any inquiry concerning this communication should be directed to Examiner Berch at telephone number (703) 308-4718.

Mark L Berch

MARK L. BERCH
PRIMARY EXAMINER
GROUP 120 - ART UNIT 122

BERCH:jd
SEPTEMBER 19, 1995